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Retinal Contrast Gain Control and Temporal Modulation Sensitivity Across the Visual Field in Glaucoma at Photopic and Mesopic Light Conditions

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Purpose. Glaucoma affects many aspects of visual performance, including adaptation, and this may depend on ambient luminance. We determine the influence of glaucoma and luminance on temporal aspects of adaptation, specifically on contrast gain control and temporal modulation sensitivity (TMS).

Methods. This case-control study included 12 glaucoma patients and 25 age-similar controls (50–70 years). Threshold perimetry was performed with a minimized testing grid (fovea and four peripheral locations). Stimuli (Goldmann size III 50 ms increment/decrement) were presented on a time-varying background with sinusoidally-modulated luminance (amplitude 60%; frequency 0–30 Hz; mean background luminance, 1 and 100 cd/m^2). TMS (2.5–30 Hz) was measured in the same locations with a sinusoidally-modulated stimulus (Goldmann size IV, 334 ms) on a steady background (1 and 100 cd/m^2).

Results. In healthy subjects, contrast sensitivity decreased with increasing background modulation frequency and increased again at very high frequencies, indicating contrast gain control. Minimum sensitivity was located between 2.5 and 20 Hz, depending on luminance and eccentricity. In glaucoma patients, the same frequency dependency was found ($P = 0.12$) but with an overall reduced sensitivity ($P = 1 \times 10^{-5}$), independent of luminance ($P = 0.20$). Decrements differentiated better between glaucoma and healthy subjects than increments ($P = 0.004$). TMS was reduced in glaucoma ($P = 5 \times 10^{-6}$) across all frequencies and luminance levels, with complete loss for high frequencies at 1 cd/m^2.

Conclusions. Contrast gain control is largely unaffected in glaucoma, suggesting intact amacrine cell function. Perimetry with decrements or a high-frequency stimulus on a low-luminance background seems best to differentiate between glaucoma and healthy subjects.

Keywords: glaucoma, contrast gain control, temporal modulation sensitivity, photopic, mesopic

The process of retinal adaptation ensures optimal visual functioning under a broad range of light and contrast levels in healthy human eyes. However, the same does not seem to be occurring in glaucomatous eyes. Glaucoma is an optic neuropathy, characterized by optic nerve head damage associated with loss of retinal ganglion cells (RGCs), which leads to loss of visual function. Questionnaire studies have shown that glaucoma patients have disproportionately more visual complaints in dimly lit and very bright environments, as well as under rapidly changing luminance conditions.[1–5] Thus far, psychophysical experiments were able to quantify poor visual performance in the dark, and to some extent, in very bright lighting. However, psychophysical data regarding visual performance of glaucoma patients under rapidly changing luminance conditions remain lacking in the literature.

Visual function loss in glaucoma usually is quantified using static automated perimetry (SAP), in which contrast detection thresholds are determined for small luminance increment targets that are projected on a background with steady luminance. Previously, we investigated the process of light adaptation in glaucoma by performing perimetry for a broad range of steady background luminances and (temporal) steps in background luminance.[6,7] Clear differences between glaucoma patients and controls were found but, due to the design of the experiments, we were not able to clarify the complaints of glaucoma patients under rapidly changing luminance conditions.

Amacrine cells are considered change detectors that respond to rapid changes in illumination.[8] These cells reduce the sensitivity of the RGCs, thus matching local contrasts of a scenery to the RGC dynamic range and, thus, preventing its saturation. This mechanism is known as contrast gain control. Despite the fact that amacrine cells are not primarily affected in glaucoma,[9,10] loss of RGCs or loss of RGC dendrites could compromise the amacrine cells through their connections with RGCs and,[11] subsequently, the contrast gain control mechanism. This might be one of the reasons for the complaints of glaucoma patients associated with rapidly changing luminance conditions and, thus, a potentially important measure of their visual function. Contrast gain control has been studied in great

detail in healthy subjects for photopic, foveal vision.[12,13] However, the same mechanism for peripheral vision, or at lower light levels, has not yet been addressed. Hood et al.[12] and Snippe et al.[13] studied the dynamics of adaptation by measuring detection thresholds for small flashing targets on a sinusoidally flickering background (probed-sinewave paradigm). The results showed that detection thresholds increased with increasing modulation frequency, that is, contrast gain control. At very high frequencies, the thresholds decreased, finally reaching the value for the unmodulated background. The absence of contrast gain control at very high frequencies could be related to flicker fusion or temporal modulation sensitivity, in which frequencies unresolved by the outer retina will not activate the amacrine cells.

Our aim was to characterize the influence of glaucoma and luminance on temporal aspects of adaptation. For this purpose, we used a paradigm that presumably addresses the contrast gain control in the inner retina.[12,13] We measured, in glaucoma patients and healthy subjects, contrast detection thresholds for luminance increment/decrement targets with the background luminance temporally modulated. As a reference, we also studied the temporal modulation sensitivity in all participants. Both experiments were performed at photopic and mesopic luminance levels and at different eccentricities.

Methods

Participants

We included 12 glaucoma patients and 25 age-similar healthy subjects, all 50 to 70 years old. Glaucoma patients were selected from the ophthalmic outpatient department of the University Medical Center Groningen (UMCG), using the visual field database of the Groningen Longitudinal Glaucoma Study (GLGS).[14] Healthy subjects were recruited by advertisement. The study was approved by the ethics committee of the UMCG (NL61403.042.17) and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent.

All participants had to have a best-corrected visual acuity (BCVA) of 0.1 logMAR or better. Glaucoma patients were required to have a clinical diagnosis of primary open angle glaucoma (POAG) with a SAP mean deviation (MD) ranging from −3 to −15 dB, as measured with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) with 30-2 grid and SITA fast strategy. When both eyes were eligible, the eye with the lower (more negative) MD value was selected. Healthy subjects were required to have an IOP below 21 mmHg; they were not allowed to have any eye abnormality or positive family history of glaucoma, as assessed by a questionnaire. They also had to have a normal mean peripapillary retinal nerve fiber layer thickness and a normal thickness of the retinal ganglion cell layer in the macular area, as assessed by optical coherence tomography (Canon HS-100 OCT, software version 4.1.0; Tokyo, Japan). Visual field defects were screened for using frequency doubling technology (FDT C20-1 screening mode; Carl Zeiss, Jena, Germany); any reproducibly abnormal test location at $P < 0.01$ was considered abnormal. A normal FDT test result, especially in a population with a low baseline risk of glaucoma (normal IOP, negative family history of glaucoma, normal OCT findings), makes the presence of glaucoma very unlikely.[15] If both eyes met the inclusion criteria, the test eye was chosen at random.

Stimulus Setup and Experimental Paradigms

Stimuli were displayed on a BenQ XL2540 monitor driven by the Psychophysics Toolbox (PTB-3)[16,17] with Octave (version 4.0.0; available in the public domain at www.gnu.org/software/octave/) on a computer running GNU/Linux (Ubuntu 16.04 LTS). Monitor resolution was set to 1920 × 1080 with a refresh rate of 240 Hz and maximum luminance of 380 cd/m^2. Luminance was measured with a Minolta luminance meter with a built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Tokyo, Japan).

Observers were positioned using a chin rest and viewed the monitor at 0.50 m. At this viewing distance, the monitor can present stimuli up to an eccentricity of 30° horizontally and 17° vertically. All tests were performed monocularly (see previous section for eye selection) with optimal correction for the viewing distance. Testing was done in a dimly lit room; the fellow eye was occluded with an eyepatch. Two luminance conditions were applied, with a mean background luminance of 1 and 100 cd/m^2 (mesopic and photopic condition). The lower luminance condition was achieved using an absorptive neutral density (ND) filter with optical density 2 (transmission 0.01; #65–817, Edmund Optics, Barrington, NJ, USA). Participants completed the testing during one visit lasting approximately 2 hours, including breaks.

The testing order of the various experimental parameters was pseudo-randomized and balanced within and between the groups. However, the photopic condition always preceded the mesopic condition; in between there was an adaptation time of at least 4 minutes.[6,18,19] All experiments were preceded by a practice run.

Experiment 1: Perimetry With a Time-Varying Background

This experiment was designed as an extension of the probed-sinewave paradigm for foveal light-adaptation dynamics as described previously.[12,13] We performed static threshold perimetry with a minimized testing grid, consisting of the fovea and four peripheral test locations located at (±9°, ±9°). For glaucoma patients, we only included a quadrant if there was a normal or near normal performance (sensitivity ≥ 25 dB) in the concerning test location on their most recent HFA test. Stimulus was a Goldmann size III, 50 ms, increment/decrement presented on a time-varying background with a sinusoidally-modulated luminance of 60% amplitude. The timing of the stimulus was random relative to the phase of the background modulation (see Discussion). We used six different modulation frequencies: 0, 1.25, 2.5, 5, 10, 20, and 30 Hz, where 0 Hz is the steady background. A fixation target was present at all times and consisted of four small rectangles (0.1° × 0.1°), located left, right, above, and below fixation, at an eccentricity of 0.5°. Contrast detection thresholds were determined using a 4-2 dB staircase procedure (as was used in the original, classic central static threshold test).[20] Contrast sensitivity (CS) was the inverse of the obtained Weber contrast (ratio of increment/decrement to background luminance at the concerning point of time with boundaries of −1 and 1) threshold.

Experiment 2: Perimetry With a Time-Varying Stimulus

In this experiment, we determined foveal and peripheral contrast sensitivity for temporally-modulated (sinusoidally-flickering) stimuli on a steady background (temporal modulation sensitivity; TMS). Stimulus size was Goldmann size IV. With size IV we had a better test–retest variability,[21] and a better visibility under the lower luminance condition, as determined during a pilot experiment. Testing grid and luminance conditions were identical to that of Experiment 1; stimulus duration was 334 ms. We used a subset (2.5, 5, 10, 20, and 30 Hz) of the frequencies used in Experiment 1. Contrast

Table 1. Characteristics of the Study Population

	Cases, $N = 12$	Controls, $N = 25$	P Value
Age, mean years (SD)	63 (5.7)	62 (5.6)	0.53
Sex, male, n (%)	11 (44%)	8 (67%)	0.35
HFA MD of the included eye (median IQR; dB)	−8.3 (−6.3 to −10.6)	-	-

detection thresholds were determined using a 3.5 to 1.5 dB staircase procedure.[22] CS was the inverse of the obtained Weber contrast threshold.

Data Analysis

We used descriptive statistics for characterizing the included participants. Mean and SD were used in case of normally distributed data, otherwise median and interquartile range (IQR). For univariable comparisons, we used a t-test or a Wilcoxon test, depending on the distributions.

For both experiments, we studied the influence of the various parameters (glaucoma or healthy subjects, temporal frequency of background (Experiment 1) or stimulus (Experiment 2), polarity (Experiment 1), eccentricity (foveal versus peripheral), and mean background luminance on the contrast sensitivity. For this, we used complete case repeated measures ANOVA, using aov in R (see below). The presence or absence of glaucoma was entered as a between-subject variable; frequency, polarity, eccentricity, and luminance were within-subject variables. Glaucoma patients were tested only in a quadrant if they showed normal or near performance on their most recent HFA test (see above); the results from the remaining peripheral test locations were averaged. For the controls, we averaged the results of the four peripheral test locations. If a stimulus was not detected (which sometimes happened at the lower luminance condition for higher frequencies), we substituted a logCS value for the particular test location, corresponding to 2 dB above maximum contrast of the perimeter. We only included frequencies in the ANOVA for which more than 75% of the subjects were able to see the stimulus at the particular frequency, for the most challenging combination of parameters (glaucoma, lower luminance, periphery). As a result, the ANOVA for Experiment 2 did not include 20 and 30 Hz; all frequencies were included in the ANOVA for Experiment 1. Inclusion of false-positive responses ('trigger-happy') was avoided by excluding the logCS corresponding to a specific data point if it was higher than the mean logCS plus 2.3 SD of the controls for the concerning test location (Chauvenet's criterion).[6,23] Results were presented graphically using the mean and SEM.

All analyses were performed using R (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria). $P \leq 0.05$ was considered statistically significant.

Results

Table 1 shows the characteristics of the included participants. Groups were similar with regard to age and sex; most patients had early or moderate glaucoma (median HFA MD −8.3 dB).

Experiment 1: Perimetry With a Time-Varying Background

Figure 1 shows the effect of the background modulation frequency on the contrast sensitivity, stratified for the presence or absence of glaucoma, eccentricity (fovea or periphery), mean background luminance, and polarity (increment or decrement). Table 2 (middle column) presents the results of the corresponding ANOVA. Contrast gain control could be observed clearly: there was a decrease in LogCS with increasing frequency. For the photopic condition, a minimum was reached at approximately 10 and 20 Hz for the fovea and periphery, respectively; for the mesopic condition, the corresponding minima were at 5 and 5 to 10 Hz, respectively. LogCS was significantly lower for glaucoma than for healthy subjects ($P = 1 \times 10^{-5}$), but contrast gain control did not differ between the groups (no significant interaction between glaucoma and frequency; $P = 0.12$). The magnitude of the contrast gain control (difference between LogCS at 0 Hz and at the minimum) was typically 0.5 and 0.3 log units for the photopic and mesopic conditions, respectively. Related to that, there was a significant interaction between frequency and luminance ($P < 2 \times 10^{-16}$). LogCS was lower in the periphery ($P < 2 \times 10^{-16}$) and this effect was slightly more pronounced in glaucoma ($P = 0.052$). Luminance had a strong effect on LogCS ($P = 2 \times 10^{-14}$), similarly for glaucoma and healthy subjects ($P = 0.20$). LogCS was greater for decrements than for increments, but only in healthy subjects in the periphery ($P = 0.004$). This implies, as can be seen in Figure 1, that the difference between healthy subjects and glaucoma is largest when the periphery is tested with decrements (Hedges' $g > 0.8$ for all frequencies at both luminances tested).

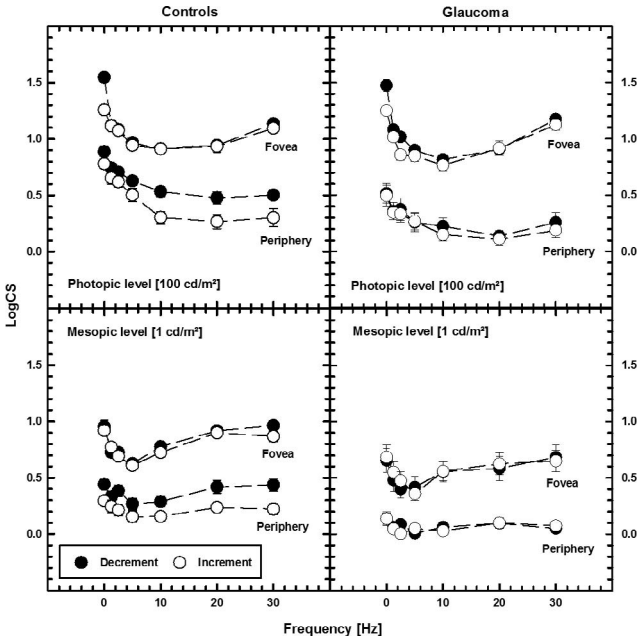

Figure 1. LogCS (mean ± 1 SE; error bars often smaller than the data points) as a function of background modulation frequency, for healthy subjects (*left column*) and glaucoma patients (*right column*), as a function of eccentricity, polarity, and mean background luminance.

Table 2. ANOVA Results for Experiment 1 (Perimetry With a Time-Varying Background; Middle Column) and Experiment 2 (Perimetry With a Time-Varying Stimulus; Last Column)

Factor	Experiment 1, *P* Value	Experiment 2, *P* Value
Eccentricity	$<2 \times 10^{-16}$	$<2 \times 10^{-16}$
Polarity	4×10^{-7}	NA
Luminance	2×10^{-14}	$<2 \times 10^{-16}$
Frequency	$<2 \times 10^{-16}$	$<4 \times 10^{-13}$
Glaucoma	1×10^{-5}	5×10^{-6}
Luminance × frequency	$<2 \times 10^{-16}$	$<2 \times 10^{-16}$
Frequency × eccentricity	$<2 \times 10^{-16}$	0.014
Polarity × eccentricity	0.001	NA
Glaucoma × eccentricity	0.052	0.001
Glaucoma × polarity	0.011	NA
Glaucoma × luminance	0.20	0.18
Glaucoma × frequency	0.12	0.016
Glaucoma × polarity × eccentricity	0.004	NA
Glaucoma × luminance × frequency	0.004	0.41

Experiment 2: Perimetry With a Time-Varying Stimulus

Figure 2 shows the contrast sensitivity for temporally modulated targets on a steady background, as a function of modulation frequency (TMS), for both groups, for fovea and periphery, and for the photopic and mesopic conditions. Table 2 (last column) presents the results of the corresponding ANOVA. Peak sensitivity was found between 5 and 10 Hz for the photopic condition and between 2.5 and 5 Hz for the mesopic condition, for both groups. In the presence of glaucoma, TMS was significantly lower ($P = 5 \times 10^{-6}$); the curves of the glaucoma patients appeared to be shifted downwards compared to those of the controls. However, there remained a significant interaction between glaucoma and frequency ($P = 0.016$) related to a somewhat larger difference between glaucoma and healthy subjects at higher frequencies. TMS was lower in the periphery than in the fovea for both groups ($P < 2 \times 10^{-16}$); this effect of eccentricity was more pronounced in glaucoma ($P = 0.001$). Luminance had a strong impact on TMS ($P < 2 \times 10^{-16}$), similarly for glaucoma and healthy subjects ($P = 0.18$). However, glaucoma patients experienced a complete loss of sensitivity for high temporal frequencies for the mesopic condition, also foveally. This finding was not detected in the ANOVA (no significant interaction between glaucoma, frequency, and luminance; $P = 0.41$), presumably because we had to exclude 20 and 30 Hz from the analysis due to missing data related to the complete loss of sensitivity for high temporal frequencies for the mesopic condition in glaucoma.

Discussion

Contrast sensitivity for small increments and decrements decreases with increasing background modulation frequency and increases again for very high frequencies, indicating contrast gain control. The minimum sensitivity is between 2.5 and 20 Hz, depending on luminance and eccentricity. For glaucoma patients, the same curve shape was found but with an overall reduced sensitivity, independent of luminance. Decrements differentiated better between glaucoma and healthy subjects than increments. Similarly, TMS was reduced in glaucoma across all frequencies and luminance levels. Glaucoma patients experienced complete loss of TMS for high temporal frequencies at low luminance.

To some extent, our findings of Experiment 1 can be compared to two earlier studies, from which we derived our methodology (see Methods of Experiment 1). Hood et al.[12] and Snippe et al.[13] assessed contrast gain control in a small group of young, healthy subjects by measuring detection thresholds for foveal increments of size 1° (10 ms) on a temporally-modulated background with a mean luminance of 2.7 cd/m^2, and for size 0.76° (7.5 ms) on a temporally-modulated background with a mean luminance of 82 cd/m^2, respectively, for a range of temporal frequencies. They reported a decrease in retinal sensitivity (increase in detection threshold) that was negligible at low temporal frequencies (below 0.3 Hz), became clearly observable around 1 Hz, and reached its maximum at approximately 10 Hz. As such, their findings were in agreement with our results; we extended their experiment to different luminances and eccentricities, to decrements, and to glaucoma. To the best of our knowledge, these extensions have not been reported previously. Importantly, the earlier studies reported a change in the detection threshold that was

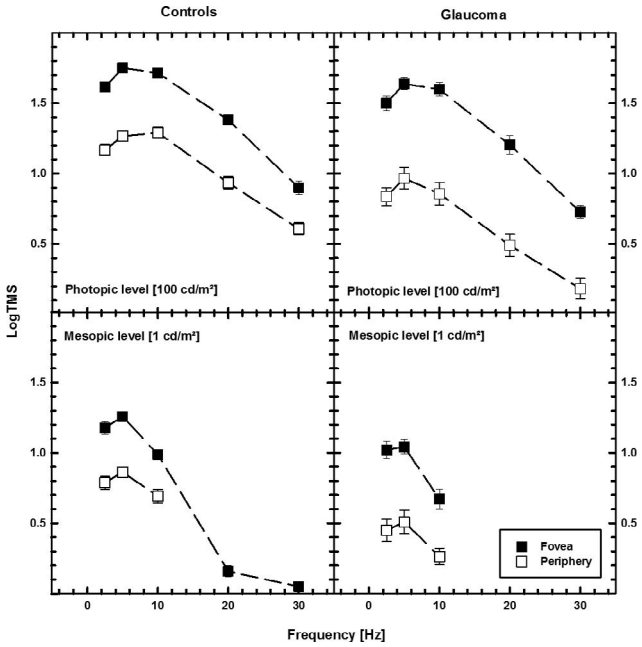

Figure 2. TMS (LogTMS; mean ± 1 SE; error bars often smaller than the data points) as a function of target modulation frequency, for healthy subjects (*left column*) and glaucoma patients (*right column*), as a function of eccentricity and mean background luminance.

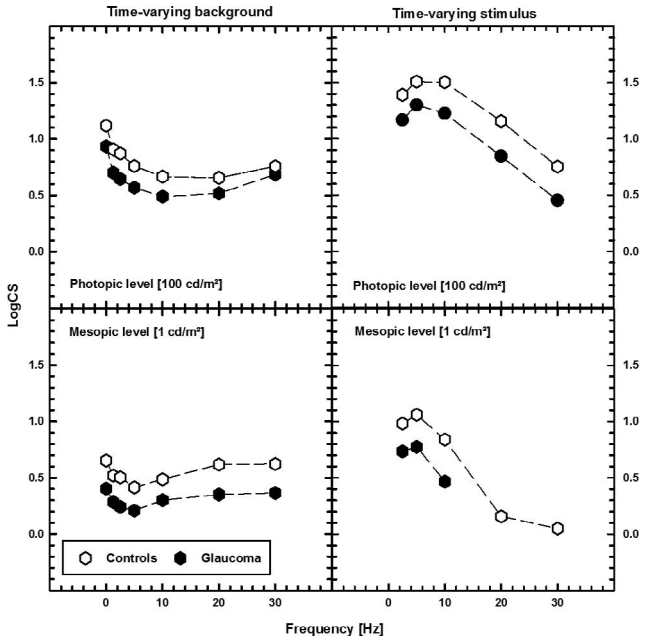

FIGURE 3. Mean LogCS (averaged over polarity and eccentricity; *left column*) and mean LogTMS (averaged over eccentricity; *right column*) as a function of background modulation frequency and stimulus frequency, respectively, for healthy subjects and glaucoma patients, as a function of mean background luminance.

dependent on the phase of the background modulation. We reanalyzed their data by replacing the detection threshold with a contrast threshold, being the threshold divided by the actual phase-dependent background luminance. The resulting contrast threshold was largely independent of the phase and, for that reason, we did not study the effect of background modulation phase separately (our stimulus onset was random in relation to the phase of the background modulation).

Our TMS results (Experiment 2) demonstrated that flicker sensitivity decreases with eccentricity. This is consistent with earlier reports.[24,25] In glaucoma, flicker sensitivity has been reported to be reduced, and this reduction is most pronounced at higher temporal frequencies and larger eccentricities.[24,26,27] This agrees with our findings (Table 2, significant interactions between glaucoma and frequency and between glaucoma and eccentricity). We extended the previous experiments to the mesopic condition and found an overall loss of flicker sensitivity with decreasing light levels, with a shift of the peak towards lower frequencies, for glaucoma and healthy subjects. Loss of flicker sensitivity with a decrease in luminance towards the mesopic level has been reported previously at a single frequency of 15 Hz in healthy subjects.[28] We did not find any study regarding loss of TMS with decreasing luminance in glaucoma.

The strengths of our study are the large sample size and wide range of conditions used compared to previous studies. This enabled us to show that contrast gain control is not just a photopic, foveal phenomenon. A weakness is the limited age range studied. This does not influence our glaucoma–healthy comparison, as we used age-similar groups. Nevertheless, it would be interesting to know if contrast gain control and TMS show a similar age dependency.

Our results indicated that the assessment of retinal functions more subtle than just sensitivity as a function of location is feasible in a clinical setting, with experiments that resemble a traditional clinical perimetric test. We demonstrated, with our time-varying background perimetry, that contrast gain control can be measured and we found clear sensitivity differences between glaucoma and healthy subjects, in both luminance conditions. Similarly, we were able to uncover differences in temporal modulation sensitivity, measured by perimetry with a time-varying stimulus, between glaucoma and healthy subjects, again in both luminance conditions. In general, as can be seen in Figure 3, the curves of the glaucoma patients resemble those of the controls shifted downwards. This would indicate that our results do not clearly favor perimetry with a time-varying background or stimulus over standard automated perimetry. However, some benefit of a time-varying stimulus could be present (Table 2; significant interaction between glaucoma and frequency), above approximately 10 Hz (Fig. 3), which agrees with earlier studies.[29,30] As argued in the Results, the benefit might be even more pronounced in the mesopic condition. We also found, for perimetry with a time-varying background, a higher sensitivity for decrements than for increments in healthy subjects, but not in glaucoma patients, in the peripheral visual field, in both luminance conditions (significant interaction between polarity, glaucoma, and eccentricity; $P = 0.004$). This indicates that, for glaucoma diagnostics, perimetry with decrements could be more effective than perimetry with increments, or the ratio between both sensitivities could convey useful information. Clearly, more work is needed to further this idea. The asymmetry itself as found in healthy subjects corroborates previously shown ON–OFF asymmetry as found for multiple visual performances (Komban et al. *J Vis* 2013;13:ARVO E-Abstract 1022).[31–38]

The fact that differences between glaucoma and healthy subjects do not clearly depend on the exact stimulus parameters (as depicted by the vertical shift of the curves in Figure 3 and the absence of clear significant interactions between glaucoma and luminance in Table 2) seems to disagree with patient experience. In a recent questionnaire study,[1] we found that glaucoma patients reported disproportionately more complaints under extreme (low, high, and changing) luminance conditions compared to controls. However, this is not a contradiction. Given the poorer performance of glaucoma patients roughly across all conditions, they will become symptomatic (that is, cross a certain minimum CS needed for reasonable vision) earliest in those situations that are most challenging for everyone, being the mesopic condition and in the presence of a time-varying background.

What do our data contribute to the knowledge with regard to visual information processing in glaucoma? Snippe et al.[13] described a temporal model for early vision that explains the dynamics of light adaptation. The model consists of a sequence of three steps: (1) a divisive light adaptation that describes the temporal characteristics of the photoreceptor responses, (2) a subtractive light adaptation (high-pass filter) that explains the attenuation of low frequencies as observed in the RGC's responses, and (3) a contrast gain control mechanism that describes the increased detection thresholds in the presence of dynamic backgrounds.[12,13] With all the caveats of linking psychophysics to anatomy and physiology, they argued that contrast gain control would be primarily a retinal phenomenon.[12,13] Indeed, the retina seems to be a plausible location for contrast gain control, as has been argued previously.[39,40] More specifically, contrast gain control has been linked to amacrine cell function.[8] Although the amacrine cells are not the primary site of glaucomatous damage,[9,10] they are closely connected to RGCs, and RGC death could potentially result in the loss of neighboring amacrine cells.[11] As can be concluded from our experiments, contrast gain control is not clearly affected in glaucoma. Similar to the study by Bierings et al.,[6] who studied static perimetry and critical flicker fusion as a function of luminance, we found a comparable reduction in sensitivity

across all conditions tested (depicted by the vertical shift of the curves of the patients compared to the controls in Fig. 3). Following the reasoning of Bierings et al.,[6] this would imply intact temporal adaptive mechanisms up to and including the retinal contrast gain control stage; a reduction in the number of RGCs suffices to explain the observations.[6]

In summary, inspired by the visual symptoms of glaucoma patients under low and changing luminance conditions, we explored differences in temporal aspects of visual function at photopic and mesopic levels between glaucoma and healthy subjects. With a time-varying background luminance, glaucoma patients showed an overall reduction in sensitivity compared to that of age-similar controls. Using retinal models described by Snippe et al.[13] and others,[6] we were able to explain our observations from loss of RGCs; we did not uncover specific deficits in other parts of the retina or visual pathways. The asymmetry we found between perimetry with increments and decrements, with the difference in sensitivity between glaucomatous and healthy eyes being more pronounced when using decrements, might have implications for the optimal design of a test that aims to differentiate between glaucomatous and healthy eyes.

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